

# Survival, metastasis and recurrence of oral cancer in relation to pathological features

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The outcome of 123 patients with squamous cell carcinoma of the oral/oropharyngeal mucosa treated by primary radical surgery and simultaneous neck dissection and followed up for a maximum of 5 years is reported and related to the pathological features of the tumour. Actuarial survival analysis showed the overall 1-year survival probability was 84%, falling to 69% at 2 years, and 65% at 5 years. For patients without lymph node metastasis, the corresponding survival probabilities were 95%, 86% and 86%, respectively; and for patients with metastasis, 71%, 52% and 44%, respectively. In all, 30 patients (24%) died of their oral cancer; 16 (13%) of local recurrence, 10 (8%) of regional recurrence and 4 (3%) of systemic metastases. In addition to lymph node metastasis, survival was related to the site and stage of the primary tumour, histological pattern of invasion, status of the resection margins and, for patients with metastasis, the number and anatomical level of positive nodes and the presence and extent of extracapsular spread. These pathological features are important indicators of tumour behaviour and should be incorporated into protocols for assessment of prognosis.

England and Wales and recently an increased incidence has been noted in younger age groups and in women (2). Despite recent advances in reconstructive surgery (3), the mortality remains high since a substantial proportion of patients with controlled locoregional disease develop systemic metastases (4) or second (metachronous) malignancies (5,6). Moreover, individual prognosis is often difficult to determine with accuracy and the relative importance of pathological staging is uncertain. Recently, we have shown how one measure of outcome, and hence prognosis (the development of regional lymph node metastases), is dependent on defined pathological criteria in the primary tumour (7). The standardisation of treatment protocols which is possible in a regional maxillofacial surgery unit, together with the relatively large numbers of cases referred, provide the opportunity to examine outcome in relation to several pathological features both of the primary and metastatic tumours. The aim of our study, therefore, was to assess the pathological significance and prognostic value of several clinical and histopathological features of oral cancer in relation to local recurrence, regional and systemic metastases and survival.

The prognosis of squamous cell carcinoma (SCC) of the intraoral and oropharyngeal mucosa is poor (1,2). Over 1800 new cases and 1100 deaths are reported each year in

## Materials and methods

### Surgical cases

A series of 123 consecutive patients undergoing surgery as the primary treatment for intraoral/oropharyngeal SCC at the Mersey Regional Centre for Maxillofacial Surgery,

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Walton Hospital, Liverpool, between October 1989, and October 1993, formed the material for the study.

The series comprised 80 males (65%) and 43 females (35%). The males had a mean age of 58 years (SD 12.8, range 30–88 years), significantly less than the mean age of 63 years (SD 13.4, range 11–81 years) of the females ( $t=1.96$ ,  $df=121$ ,  $P=0.049$ ). None of the patients had received preoperative radiotherapy, chemotherapy, or previous surgery other than routine dentoalveolar procedures and recent diagnostic biopsy.

In the series, clinical T stage (8) was significantly related to site (8) with a high frequency of T<sub>4</sub> tumours sited on the alveolar ridge and floor of the mouth ( $\chi^2=46.90$ ,  $df=15$ ,  $P<0.0001$ ). Moreover, tumour site was related to sex such that the male:female ratios were 2.3:1 and 2.2:1 for tumours of the tongue and floor of mouth, respectively, whereas the ratios were 0.5:1 and 1.2:1 for tumours of the alveolar ridge and buccal mucosa, respectively ( $\chi^2=11.42$ ,  $df=5$ ,  $P=0.044$ ).

Eighty-four patients (68%) underwent resection of the primary tumour with a simultaneous ipsilateral neck dissection, and in the remaining 39 patients (32%), the neck dissection was bilateral. Thus, a total of 123 primary tumours and 162 neck dissections (19 (12%) radical procedures, 77 (48%) full functional procedures, 66 (41%) supraomohyoid procedures) were available for histological assessment.

Postoperative radical radiotherapy was employed on the basis of pathological staging using the following criteria:

- 1 Involved or close (within 5 mm) resection margins at the primary site.
- 2 Two or more positive cervical lymph nodes.
- 3 One or more cervical lymph nodes showing extracapsular spread.

Of the 123 patients, 65 (52%) were found to have one or more of these features. The radiotherapy (external beam, 60–65 Gy fractionated over 6 weeks) was started, whenever possible, within 6 weeks of operation. Patients were reviewed at regular intervals. At the time of analysis, all patients had at least 1-year follow-up. Status at last contact was recorded as one of the following:

- 1 Alive and well with no signs of local or regional SCC, nor systemic metastases.
- 2 Alive with a further intraoral (metachronous) primary SCC.
- 3 Alive with recurrent local or regional SCC or systemic metastases.
- 4 Dead of local or regional recurrent SCC or systemic metastases.
- 5 Dead of other malignancy, with no signs of locoregional or systemic SCC.
- 6 Dead of other cause, with no signs of locoregional or systemic SCC.

For categories 2–6, above, both the disease-free interval (from time of operation to time of diagnosis of recurrent/further SCC) and survival were measured to the nearest month. Stomal recurrence after tracheostomy was classed as a local recurrence.

## Pathological assessment

The surgical specimens were submitted to the Oral Pathology Diagnostic Service at Liverpool University Dental Hospital, where all the gross dissections and histological assessments were made by a single pathologist (JAW). Two features were recorded in respect of the primary tumour: the histological pattern of invasion and the integrity of the surgical margins. The histological pattern of invasion (9,10) was classed as unfavourable when the advancing front was poorly defined and composed of individual or narrow cords and small islands of tumour cells. The surgical resection margins were assessed routinely (11) and classified histologically as:

- 1 Involved by carcinoma (microscopic cut-through).
- 2 Close—carcinoma within 5 mm of the surgical margin.
- 3 Clear of carcinoma, but with dysplasia of the mucosa.
- 4 Clear of carcinoma and without dysplasia.

Lymph nodes were identified by visual inspection and palpation, and were dissected out from the gross specimen in five anatomical levels (level I: submandibular/submental; levels II–IV: superior, mid- and inferior cervical; level V: posterior triangle). All nodes were processed routinely for paraffin embedding and staining by haematoxylin and eosin (H&E). Initial histological assessment was made on a single (hilar) section, with examination of step-serial sections in selected nodes. Metastatic deposits measuring 3 mm or less were defined as micrometastases (12). Further details of the pathological assessment are presented elsewhere (7).

## Statistical methods

Survival probability was calculated using the actuarial (life table) method with comparisons by the Wilcoxon test. Pearson's  $\chi^2$  test with Yates' correction for  $2 \times 2$  tables,  $\chi^2$  test for trend, and two-sample  $t$  test were used in the analysis of other clinical and histological data. The analyses were performed using the SPSS-PC package on a microcomputer. In each case, the test statistic ( $\chi^2$ ,  $\chi^2_{\text{trend}}$ , or  $t$ ), degrees of freedom ( $df$ ) and  $P$  value are given.

## Results

### Pathological assessment of primary tumours

#### Pattern of invasion

An unfavourable pattern of invasion was seen in 73 (59%) of the primary tumours. There was a significant difference in its frequency in relation to both tumour site and T stage ( $\chi^2=11.37$ ,  $df=5$ ,  $P=0.044$ ;  $\chi^2=17.80$ ,  $df=3$ ,  $P=0.00048$ , respectively). An unfavourable pattern was more frequent in tumours of the tongue (75%), oropharynx (69%) and floor of mouth (57%), and least frequent in tumours of the alveolar ridge (27%). Only 30% of T<sub>1</sub> tumours had an unfavourable pattern, compared with 61–77% of T<sub>2</sub>–T<sub>4</sub> tumours.

### *Surgical resection margins*

The surgical resection margins were involved by carcinoma in three cases (2%) and were classed as close in 24 cases (20%). There was a significant difference in the frequency of involved/close margins in relation to tumour stage and pattern of invasion, but not to tumour site. Of the 27 involved/close margins, 19 (70%) were in T<sub>3</sub>/T<sub>4</sub> tumours and the remaining eight were in T<sub>2</sub> tumours ( $\chi^2=25.16$ ,  $df=1$ ,  $P=0.0028$ ). Of the 27 involved/close margins, 25 (93%) were in tumours showing an unfavourable pattern of invasion ( $\chi^2=17.50$ ,  $df=3$ ,  $P=0.00055$ ).

The resection margins were dysplastic in 21 tumours (17%), mainly of the tongue, floor of the mouth and oropharynx. However, there were no significant differences in the frequency of dysplastic margins in relation to tumour site or stage.

### **Pathological assessment of neck dissections**

#### *Lymph node recovery*

The average number of lymph nodes recovered from each of the three types of surgical neck dissection specimens was as follows:

Radical ( $n=19$ ):	47 (SD = 17.1, range 22–96)
Functional ( $n=77$ ):	32 (SD = 10.4, range 15–56)
Supraomohyoid ( $n=66$ ):	20 (SD = 7.5, range 7–39)

In total, 4633 lymph nodes were examined histologically, and 199 (4.3%) were positive for metastatic carcinoma.

#### *Frequency of positive cervical lymph nodes*

Metastasis was diagnosed in 56 (46%) of the 123 patients. Five patients had bilateral metastatic spread. Hence, 61 neck dissections contained positive nodes.

There was a significant difference in the frequency of positive nodes in relation to sex but not to age. Of the 56 patients with positive necks, 43 (77%) were male compared with 37 males (55%) among the 67 patients without metastasis ( $\chi^2=6.24$ ,  $df=1$ ,  $P=0.012$ ). Also, there was a significant difference in the frequency of metastasis in relation to T stage and histological pattern of invasion of the primary tumour, but not to tumour site (Table I). Metastasis occurred in 8 (24%) of the 33 T<sub>1</sub> tumours, in 23 (53%) of the 43 T<sub>2</sub> tumours, in 5 (45%) of the 11 T<sub>3</sub> tumours and in 20 (56%) of the 36 T<sub>4</sub> tumours ( $\chi^2=8.59$ ,  $df=3$ ,  $P=0.035$ ). Metastasis occurred in 51 (70%) of the 73 tumours with an unfavourable pattern and in only 5 (10%) of the 50 tumours without an unfavourable pattern ( $\chi^2=40.50$ ,  $df=1$ ,  $P<0.0001$ ).

#### *Number and position of positive nodes*

In the 61 positive neck dissections, the number of positive nodes per dissection ranged from 1 to 20, (mean 3.3, SD 3.94, median 2) but 39 dissections (64%) contained only one or two positive nodes. In 12 dissections (from 11

patients), some of the positive nodes were partially fused (matted).

In 38 (62%) of the 61 positive dissections, the positive node(s) were confined to a single anatomical level, but one dissection showed involvement of all five anatomical levels, and in another 11 dissections, nodes were involved at three or four different levels.

The highest level of involvement was level I in 19 dissections (31%), level II in 23 dissections (38%), level III in nine dissections (15%), level IV in seven dissections (11%) and level V in only three dissections (5%).

In 12 (20%) of the 61 positive dissections (and in 9 (16%) of the 56 positive patients), metastatic disease was present only as micrometastases, involving one node in each of eight dissections and 2–4 nodes in the remaining four dissections.

#### *Extracapsular spread of metastatic carcinoma*

Extracapsular spread (ECS) was evident during the macroscopic assessment in 22 dissections (from 21 patients). In nine of these, the ECS involved adjacent anatomical structures. In the gross specimen, two dissections showed involvement of the skin of the upper neck, another two showed invasion of the sternocleidomastoid and/or the digastric muscles, and a further two dissections showed involvement of the muscle fascia. Eight dissections showed invasion of the internal jugular and/or the anterior facial veins. In five of these, ulceration of the intima of the vein with thrombosis was detected histologically. Histological evidence of ECS was present in a further 16 dissections (from 14 patients). Islands of carcinoma were seen within the immediate perinodal fibroadipose tissue in 14 dissections and, in another two dissections, ECS was confined to microscopic permeation/embolisation of the perinodal lymphatics. Hence, in total, ECS was present in 38 (62%) of the 61 positive dissections (macroscopic in 22, microscopic in 16), and in 35 (63%) of the 56 positive patients (macroscopic in 21, microscopic in 14).

### **Clinical outcome**

#### *Survival probability*

The status of patients at last contact is shown in Table II. Actuarial survival analysis showed the overall 1-year survival probability was 84%, falling to 69% at 2 years and 65% at 5 years (Fig. 1). For patients without histological lymph node metastasis, the 1-year survival probability was 95%, falling to 86% at 2 years and then remaining constant to 5 years. In patients with positive neck metastasis, the 1-year survival probability was 71%, falling to 52% at 2 years and 44% at 5 years (Fig. 2). The difference in survival probability between the non-metastatic and metastatic groups was highly significant (Wilcoxon test,  $\chi^2=17.48$ ,  $df=1$ ,  $P<0.001$ ).

Over the period of the study, 49 (40%) of the 123 patients died. As shown in Table II, oral cancer was the direct cause of death in 30 patients (24%). In the 16 patients who died of recurrent disease in the mouth, the

**Table I.** Frequency of lymph node metastasis and death from squamous carcinoma in relation to site and stage of primary tumour

Tumour site	Tumour stage				All stages
	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	
Oral tongue	7 (1 D)	18 (9 D)	6 (2 D)	5 (3 D)	36 (15 D)
	2 M+(1 D)	10 M+(7 D)	4 M+(2 D)	4 M+(3 D)	20 M+(13 D)
	5 M-(0 D)	8 M-(2 D)	2 M-(0 D)	1 M-(0 D)	16 M-(2 D)
Floor of mouth	14 (0 D)	12 (1 D)	0	11 (4 D)	37 (5 D)
	5 M+(0 D)	7 M+(1 D)		7 M+(4 D)	19 M+(5 D)
	9 M-(0 D)	5 M-(0 D)		4 M-(0 D)	18 M-(0 D)
Oropharynx	4 (0 D)	5 (1 D)	4 (0 D)	3 (1 D)	16 (2 D)
	1 M+(0 D)	3 M+(1 D)	1 M+(0 D)	3 M+(1 D)	8 M+(2 D)
	3 M-(0 D)	2 M-(0 D)	3 M-(0 D)		8 M-(0 D)
Retromolar trigone	2 (0 D)	1 (1 D)	1 (0 D)	2 (1 D)	6 (2 D)
		1 M+(1 D)		2 M+(1 D)	3 M+(2 D)
	2 M-(0 D)		1 M-(0 D)		3 M-(0 D)
Alveolar ridge	1 (0 D)	1 (0 D)	0	13 (4 D)	15 (4 D)
				3 M+(1 D)	3 M+(1 D)
	1 M-(0 D)	1 M-(0 D)		10 M-(3 D)	12 M-(3 D)
Buccal mucosa	5 (0 D)	6 (0 D)	0	2 (2 D)	13 (2 D)
		2 M+(0 D)		1 M+(1 D)	3 M+(1 D)
	5 M-(0 D)	4 M-(0 D)		1 M-(1 D)	10 M-(1 D)
All sites	33 (1 D)	43 (12 D)	11 (2 D)	36 (15 D)	123 (30 D)
	8 M+(1 D)	23 M+(10 D)	5 M+(2 D)	20 M+(11 D)	56 M+(24 D)
	25 M-(0 D)	20 M-(2 D)	6 M-(0 D)	16 M-(4 D)	67 M-(6 D)

D = dead of local or regional squamous carcinoma or distant metastases

M+ = lymph node metastasis present

M- = lymph node metastasis absent

disease-free interval ranged from 1 month to 18 months (mean 6.3, SD 4.4, median 5.5), and survival ranged from 3 months to 22 months (mean 9.4, SD 5.8, median 7.5). In the ten patients who died of recurrent disease in the neck, the disease-free period ranged from 1 month to 13 months (mean 5.8, SD 4.4, median 4), and survival ranged from 1 month to 18 months (mean 8.1, SD 5.5, median 7). In the four patients who died of systemic metastases, the disease-free interval was longer (range 12–41 months, mean 22.5, SD 12.8, median 18.5), and survival ranged from 20 months to 45 months (mean 26.8, SD 12.2, median 21).

In the five patients developing metachronous intraoral carcinomas, the disease-free interval range from 7 months to 46 months (mean 29.4, SD 15.9, median 30). Of these

five patients, four had dysplasia of the margins of the index primary tumour.

Three of the 19 deaths from other causes were caused by malignant tumours at other sites (colon, stomach and nasopharynx), unrelated to the index tumour as verified by clinicopathological examination.

#### Comparison of surviving and non-surviving patients

The group of 30 patients who died of oral cancer was compared with the remaining 93 patients. There were no significant differences in sex or mean age. However, as shown in Table I, there were differences in relation to tumour site, tumour stage and histological metastatic

**Table II.** Status of patients at last contact

Status	Patients with positive neck dissection	Patients with negative neck dissection	All patients
Dead of SCC	24/56 (41%)	6/67 (9%)	30/123 (24%)
at primary site	12/56 (21%)	4/67 (6%)	16/123 (13%)
regional metastases	10/56 (18%)	0/67 (0%)	10/123 (8%)
systemic metastases	2/56 (4%)	2/67 (3%)	4/123 (3%)
Dead of other cause	7/56 (13%)	12/67 (18%)*	19/123 (15%)
Alive with recurrent SCC	1/56 (2%)	0/67 (0%)	1/123 (1%)
Alive with metachronous SCC	1/56 (2%)	4/67 (6%)	5/123 (4%)
Alive and well	23/56 (41%)	45/67 (67%)	68/123 (55%)

\* Includes three patients dead of other malignancy

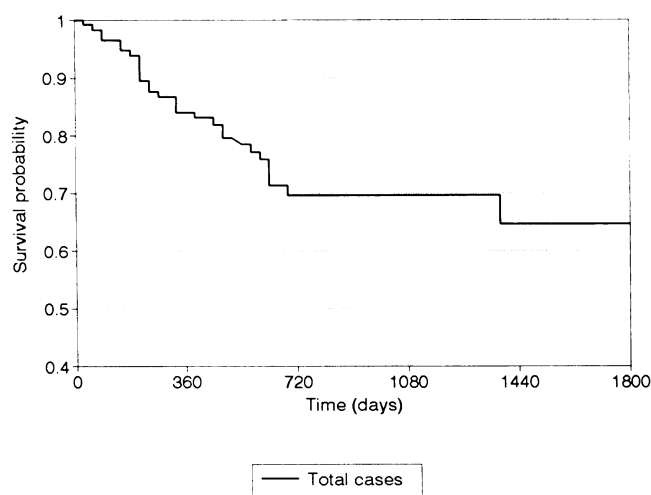


Figure 1. Actuarial survival probability for all patients.

status. Of the 36 patients with tongue tumours, 15 (42%) had died of SCC compared with 13–33% of patients with tumours at other sites ( $\chi^2 = 10.30$ ,  $df = 5$ ,  $P = 0.062$ ). Only 1 (3%) of the 33 patients with T<sub>1</sub> tumours had died of SCC compared with 18–42% of cases with T<sub>2</sub>–T<sub>4</sub> tumours ( $\chi^2 = 14.51$ ,  $df = 3$ ,  $P = 0.0022$ ). Of the 56 patients with regional lymph node metastasis, 24 (43%) were dead of SCC compared with only 6 (9%) of the 67 patients without nodal metastasis ( $\chi^2 = 19.01$ ,  $df = 1$ ,  $P < 0.0001$ ).

There were also significant differences between surviving and non-surviving patients in relation to the pattern of invasion in the primary tumour and to the presence of tumour at or near the resection margins. Of the 73 cases with an unfavourable pattern of invasion, 27 (37%) were dead of SCC, compared with only 3 (6%) of the 47 cases without an unfavourable pattern ( $\chi^2 = 15.45$ ,  $df = 1$ ,  $P < 0.0001$ ). All three cases with involved margins

and 13 (54%) of the 24 cases with close margins were dead of SCC, compared with 14 (15%) of the 96 cases with clear margins ( $\chi^2 = 26.14$ ,  $df = 3$ ,  $P < 0.0001$ ).

#### Neck pathology in relation to survival

There were significant differences in the proportion of patients alive at the end of the study in relation to the number of positive nodes ( $\chi^2_{\text{trend}} = 9.88$ ,  $df = 1$ ,  $P = 0.0017$ ); the number of involved anatomical levels ( $\chi^2_{\text{trend}} = 4.15$ ,  $df = 1$ ,  $P = 0.042$ ); the highest anatomical level of involvement ( $\chi^2_{\text{trend}} = 8.35$ ,  $df = 1$ ,  $P = 0.0039$ ); and the presence of ECS ( $\chi^2 = 10.87$ ,  $df = 1$ ,  $P = 0.00098$ ).

Of the 21 patients with macroscopic ECS, 13 (62%) were dead of SCC (five of intraoral recurrence, seven of neck recurrence and one of systemic metastases), 1 (5%) was alive with neck recurrence, 4 (19%) had died of other causes, and only 3 (14%) were alive and well. Of the nine patients with macroscopic ECS involving adjacent structures, only one was alive at the end of the study and six had died of neck recurrence. Of the twelve patients with microscopic ECS to perinodal fibroadipose tissue, 7 (58%) had died of SCC (three of intraoral recurrence, three of neck recurrence, and one of systemic metastases), 1 (8%) had died of other cause, 1 (8%) was alive with metachronous oral cancer, and 3 (25%) were alive and well. Both patients with microscopic ECS limited to the perinodal lymphatics were alive and well. Of the 21 patients with no evidence of ECS, only 4 (19%) had died of SCC (all intraoral recurrences), 2 (10%) had died of other causes, and 15 (71%) were alive and well. Of the ten patients who died of SCC in the neck, all had evidence of ECS.

## Discussion

The Regional Centre for Maxillofacial Surgery at Walton Hospital (MFU) receives referrals of a large number of mouth cancers in the geographic area of the former Mersey Regional Health Authority. Over the last 5 years, a standard treatment protocol has been adopted and the majority of patients have undergone radical resection of the primary tumour and simultaneous neck dissection, with postoperative radical radiotherapy for those patients satisfying strict criteria after pathological staging. In all cases, the pathological reporting of the resected specimens has adhered to a protocol for the laboratory dissection and histological sampling of the total specimen performed by a single pathologist in the Oral Pathology Laboratories of the Liverpool University Dental Hospital. The combination of standardised protocols both for surgical management and for pathological reporting provided the opportunity to conduct an outcome audit of a series of over 100 cases in which the variables associated with multicentre studies are reduced to a minimum. Moreover, the systematic audit of outcome in such a series provides important evidence, not only concerning the efficacy of the management protocols adopted by the MFU, but also allows the identification of those features in the patho-

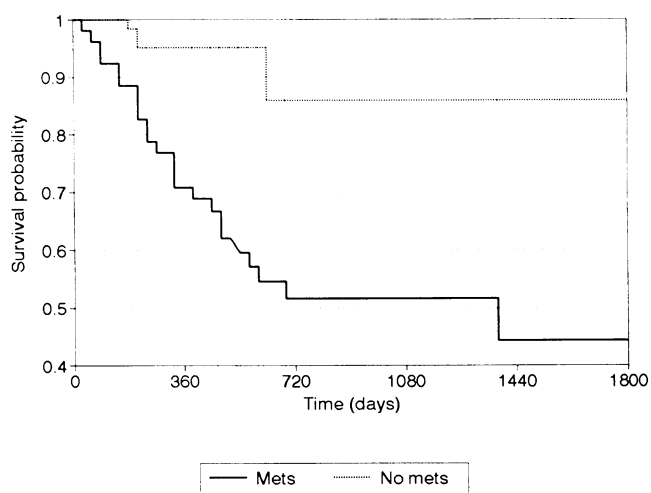


Figure 2. Actuarial survival probability classified by histological metastatic status of cervical lymph nodes (mets = patients with nodal metastasis; no mets = patients with no evidence of metastasis).

logical report which correlate with tumour behaviour and which can, therefore, serve as important prognostic indicators. This study, therefore, advances the understanding of the pathology of oral cancer by identifying particular clinicopathological features in the primary presentation and subsequent surgical resection which correlate with the documented clinical outcomes of metastasis, recurrence and survival.

The period of the study was 4 years for the accession of new cases and a maximum of 5 years for review. The use of survival analysis (13), as opposed to merely calculating the proportions surviving to a given time, makes best use of the information, and allows for censoring where appropriate (ie dead of other cause, alive at end of study, or lost). Although the review period is short for cases accessioned late in the study, so that further systemic metastases and metachronous tumours may occur over the next few years (4,6,14,15), it is also widely reported that most local and regional recurrences are diagnosed within 1 year of operation (16–19). This suggests that the findings reported at this stage are likely to provide a close indication of ultimate outcome for the series as a whole.

Our results confirm the well-established relationship between cervical node metastasis and reduced rate of survival. In our study, the 5-year probability of survival reduced from 86% among patients without cervical metastasis to 44% in patients with metastasis (Fig. 2). Of the 30 patients dying of oral cancer, 24 had cervical metastases. Moreover, our results indicate that in 50% of these patients (ie with cervical metastasis), recurrent carcinoma developed initially at the site of the primary tumour. This strongly suggests that the poor prognosis experienced by patients with positive necks has a multifactorial origin. Thus, our results show that cervical metastases are more frequent in large tumours and in tumours with a histologically unfavourable pattern of invasion. Furthermore, our data indicate that such tumours are more likely to show involved or close resection margins. As shown by others, failure to control such tumours may be dependent on systemic factors in host resistance (20) including a diminished immune response, particularly affecting the ability to mount an adequate NK cellular response (21).

Several recent reports have suggested that the improved outcome consequent on adjuvant radiotherapy diminishes the prognostic importance of pathological staging (extent of regional metastasis, presence of ECS) in oral cancer (17,22,23). Our findings do not support this. In the present study, pathological staging was used to identify patients requiring adjuvant radiotherapy. All patients with ECS, even if present only at the microscopic level, received postoperative radiotherapy; yet the prognosis of this group, as a whole, remained poor. Of the nine cases in which ECS involved adjacent anatomical structures, only one patient was alive and well at the end of the study. Furthermore, our results clearly indicate the high prognostic value of the number of nodes involved by metastases, their anatomical level and the number of

anatomical levels containing metastatic deposits. One factor possibly related to poor prognosis of patients with extensive neck disease may be the timing of the start of radiotherapy (17,22). The present study can be regarded as a preliminary audit in this respect, providing indirect support for starting radiotherapy as soon as possible and ideally within 3 or 4 weeks of operation rather than the current 6 weeks.

Several features of the primary tumour had a significant bearing on outcome. These were site, stage, histological pattern of invasion and status of the resection margins. Not surprisingly, our results show that these factors are interrelated. Hence, it is important that the extent of the resection is based on detailed histological invasive-front grading of the biopsy specimen (9). Although intraoperative frozen sections were not used routinely in our protocols, the incidence of involved/close margins was low given the relatively large number of T<sub>3</sub> and T<sub>4</sub> tumours. Where surgical margins were unsatisfactory, this was usually because the tumour involved or approached the deep muscle rather than mucosal margins. Hence, any recurrences were deep-seated, under the reconstruction and tended to be extensive at detection.

Of the four patients who died of systemic metastases, two had no evidence of regional lymphatic spread. Both had T<sub>4</sub> tumours of the alveolar ridge and developed bone pain and fractures as the first signs of systemic disease. Although the number of cases is too few to allow any firm conclusions, in both patients, extensive involvement of alveolar bone, with an 'infiltrative' rather than an 'erosive' pattern (24), had been observed in the primary tumour.

Micrometastases (12) were observed in 9 (7%) of the 123 patients and in 12 (20%) of the 61 positive neck dissections. We believe that such a high incidence of micrometastases gives strong support for the continued use of elective neck dissection for tumours at high-risk sites.

This study of oral cancer confirms that the occurrence of regional lymph node metastasis has a profound effect on survival and shows the critical importance of early (T<sub>1</sub>) diagnosis of the primary tumour (Table I). Furthermore, our results show that certain pathological features of the primary tumour (the pattern of invasion) and of the neck dissection (extent and level of nodal involvement and presence and extent of ECS) are important indicators of tumour aggression and can thus be used to improve the accuracy of prognosis.

## References

- 1 Boyle P, Macfarlane GJ, Maisonneuve P, Zheng T, Scully C, Tedesco B. Epidemiology of mouth cancer in 1989: a review. *J R Soc Med* 1990; 83: 724–30.
- 2 Hindle I, Nally F. Oral cancer: a comparative study between 1962 and 1967 and 1980 and 1984 in England and Wales. *Br Dent J* 1991; 170: 15–20.
- 3 Vaughan ED, Bainton R, Martin IC. Improvements in

- morbidity in mouth cancer using microvascular free flap reconstruction. *J Craniomaxillofac Surg* 1992; 20: 132-4.
- 4 Vikram B, Strong EW, Shah J, Spiro R. Failure at distant sites following multimodality treatment for advanced head and neck cancer. *Head Neck Surg* 1984; 6: 730-33.
  - 5 Vikram B, Strong EW, Shah J, Spiro R. Second malignant neoplasms in patients successfully treated with multimodality treatment for advanced head and neck cancer. *Head Neck Surg* 1984; 6: 734-7.
  - 6 Carr RJ, Langdon JD. Multiple primaries in mouth cancer—the price of success. *Br J Oral Maxillofac Surg* 1989; 27: 394-9.
  - 7 Woolgar JA. Lymph node metastasis in oral cancer. PhD Thesis. The University of Liverpool, 1994.
  - 8 American Joint Committee on Cancer. Head and neck sites. In: Beahrs OH, Henson DE, Hutter RVP, Myers MH, eds. *Manual for Staging of Cancer*. 3rd Edition. Philadelphia: JB Lippincott, 1988: 27-38.
  - 9 Bryne M, Koppang H, Lilleng R, Kjaerheim A. Malignancy grading of deep invasive margins of oral squamous cell carcinomas has high prognostic value. *J Pathol* 1992; 166: 375-81.
  - 10 Anneroth G, Batsakis J, Luna M. Review of the literature and a recommended system of malignancy grading in oral squamous cell carcinomas. *Scand J Dent Res* 1987; 95: 229-49.
  - 11 Barnes L, Johnson JT. Pathologic and clinical considerations in the evaluation of major head and neck specimens resected for cancer. Part 1. *Pathol Annu* 1986; 21: 173-250.
  - 12 Van den Brekel MWM, Stel HV, van der Valk P, van der Waal I, Meyer CJLM, Snow GB. Micrometastases from squamous cell carcinoma in neck dissection specimens. *Eur Otorhinolaryngol* 1992; 249: 349-53.
  - 13 Altman DG. Analysis of survival times. In: Altman DG, ed. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1991: 365-95.
  - 14 Kotwall C, Sako K, Razack MS, Rao, V, Bakamjian V, Shedd DP. Metastatic patterns in squamous cell carcinoma of the head and neck. *Am J Surg* 1977; 154: 439-42.
  - 15 Leemans CR, Tiwari R, Nauta JJP, van der Waal I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. *Cancer* 1993; 71: 452-6.
  - 16 Langdon JD, Harvey PW, Rapidis AD, Patel MF, Johnson NW, Hopps R. Oral cancer: the behaviour and response to treatment of 194 cases. *J Maxillofac Surg* 1977; 5: 221-37.
  - 17 Vikram B, Strong EW, Shah JP, Spiro R. Failure in the neck following multimodality treatment for advanced head and neck cancer. *Head Neck Surg* 1984; 6: 724-9.
  - 18 Vikram B, Strong EW, Shah JP, Spiro R. Failure at the primary site following multimodality treatment for advanced head and neck cancer. *Head Neck Surg* 1984; 6: 720-23.
  - 19 Foote RL, Olsen KD, Davis D *et al.* Base of tongue carcinoma: patterns of failure and predictors of recurrence after surgery alone. *Head Neck* 1993; 15: 300-307.
  - 20 Scully C. The immunology of cancer of the head and neck with particular reference to oral cancer. *Oral Surg Oral Med Oral Pathol* 1982; 53: 157-67.
  - 21 Wang MB, Lichtenstein A, Mickel RA. Hierarchical immunosuppression of regional lymph nodes in patients with head and neck squamous cell carcinoma. *Otolaryngol Head Neck Surg* 1991; 105: 517-27.
  - 22 Leemans CR, Tiwari RM, van der Waal I, Karim ABMF, Nauta JJP, Snow GB. The efficacy of comprehensive neck dissection with or without postoperative radiotherapy in nodal metastases of squamous cell carcinoma of the upper respiratory and digestive tracts. *Laryngoscope* 1990; 100: 1194-8.
  - 23 Johnson JT, Barnes EL, Meyers EN, Schram VL, Borochoy D, Sigler BA. The extracapsular spread of tumors in cervical node metastasis. *Arch Otolaryngol* 1981; 107: 725-9.
  - 24 Slootweg PJ, Muller H. Mandibular invasion by oral squamous cell carcinoma. *J Craniomaxillofac Surg* 1989; 17: 69-74.

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